Refine Search

Search Results -

Terms	Documents
L3 and sphingomyelin	4

Database: US Pre-Grant Publication Full-Text Database; US Patents Full-Text Database; US OCR Full-Text Database; EPO Abstracts Database; JPO Abstracts Database; Derwent World Patents Index; IBM Technical Disclosure Bulletins

Search: L4

Refine Search | Recall Text | Clear | Interrupt

Search History

DATE: Friday, March 04, 2005 Printable Copy Create Case

Set Name side by side	Query	Hit Count	Set Name result set
DB=USPT,EPAB,JPAB,DWPI,TDBD; PLUR=YES; OP=OR			
L4	L3 and sphingomyelin	4	L4
L3	sphingosome and (vinca or vincristine oe vinblastine or vinorelbine or vindestine)	7	L3
L2	sphingosome	13	L2
L1	sphingosome same (vinca or vincristine oe vinblastine or vinorelbine or vindestine)	0	L1

END OF SEARCH HISTORY

L3: Entry 5 of 7 File: USPT Apr 21, 1998

DOCUMENT-IDENTIFIER: US 5741516 A
TITLE: Sphingosomes for enhanced drug delivery

Abstract Text (1):
Liposomal formulations having extended circulation time in vivo and increased drug retention are comprised of sphingomyelin and cholesterol and have an acidic intraliposomal pH. The formulations have enhanced stability and thus are used in methods which provide improved drug delivery and more effective treatment. The delivery of ciprofloxacin, and alkaloid drugs, particularly swainsonine, vincristine and vinblastine, is significantly improved.

Brief Summary Text (2):
Liposomal formulations of therapeutically active drugs have significant advantages over drugs injected in free form. Weinstein, Liposomes: From Biophysics to Therapeutics, (Ostro, M. J., ed.), Marcel Dekker, Inc., NY, pp. 277-338, (1987). For example, liposomal formulations of the anti-cancer alkaloid vincristine have greater efficacy against L1210 leukemia cells than does free vincristine and have reduced collateral toxicity. Mayer et al., Cancer Chemother. Pharmacol. 33:17-24 (1993) and Mayer et al., Cancer Res. 50:575-579 (1990). The development of liposomal formulations of therapeutic agents with clinical and/or pharmaceutical potential depends on the liposome/drug combination possessing both biological efficacy and long-term chemical stability. In general, the efficacy of a liposomal agent can be improved by increasing both the liposome circulation lifetime and the ability of the liposome to retain the encapsulated drug. Mayer, ibid, and Boman et al., Cancer Res. 54:2830-2833 (1994). Therefore, much effort has focused on the development of liposomal formulations of therapeutic compounds having both extended circulation times and enhanced drug retention.

Brief Summary Text (4):
For example, vincristine can be loaded efficiently into liposomes by a pH gradient-dependent encapsulation procedure which employs an intraliposomal pH of 4.0. Mayer et al., Biochim. Biophys. Acta 1025:143-151 (1990) and Mayer et al., Cancer Res. 50:575-579 (1990). The work with liposomal vincristine has been based on vesicles containing phosphatidylcholine (PC), usually egg PC or distearoyl-PC, and cholesterol. Mayer et al., 1993, supra. Increased anti-tumor efficacy of liposomal vincristine occurs when the in vivo retention of vincristine in the liposomes is increased using a 100-fold larger transmembrane pH gradient (i.e. intraliposomal pH =2.0). Boman et al., supra. However, at this pH the acid-hydrolysis of the PC component of the liposomes occurs at a significant rate and severely limits the chemical stability of the liposomes. In particular, the fatty acid carboxyl esters at positions sn-1 and sn-2 are especially susceptible to acid-hydrolysis to produce lyso-PC and free fatty acids. Grit et al., Chem. Phys. Lipids 64:3-18 (1993). Liposomes containing significant proportions of lyso-PC are more permeable to solutes, and therefore would be unsuitable as drug delivery vehicles.

Brief Summary Text (8):
The present invention provides a liposomal composition for delivery of a therapeutic compound to a mammalian host. The composition comprises a liposome having one or more membranes which comprise sphingomyelin and cholesterol, a liposomal interior having a pH less than that of the liposomal exterior, and a

therapeutic compound contained in the liposome for delivery to the host. The sphingomyelin and cholesterol are typically present at a molar ratio from 75/25 mol%/mol%, respectively, to 30/50 mol%/mol%, respectively and in a preferred example at a ratio of about 55/45, mol%/mol%, respectively. The lipophilic therapeutic compound may be an alkaloid, such as vincristine, vinblastine, swainsonine, or etoposide or a prodrug thereof. The therapeutic may also be the antibacterial ciprofloxacin or derivative thereof. The drug, such as vincristine, may be present at a drug to lipid ratio of approximately 0.01/1.0 to 0.2/1.0 (wt/wt). Swainsonine may be present at a drug to lipid ratio of 0.01:1.1 to 0.5:1.0 (mol:mol). Targeting ligands and other lipids may also be present as components of the liposome so long as they do not adversely affect the stability of the drug and liposome. The liposomes may be unilamellar or multilamellar, and will typically have mean diameters of about 0.05 microns to 0.45 microns, and more preferably about 0.05 microns to 0.2 microns. The interior of the liposome will typically have at a pH of approximately pH 2 to pH 5, e.g., comprising a citrate buffer at about pH 4.

Brief Summary Text (10):
The invention also provides methods for enhanced delivery of a lipophilic therapeutic compound such as an alkaloid to a host for treatment. The host in need of the treatment, such as a patient suffering from a tumor, is administered the liposomal composition which comprises a liposome having one or more membranes which comprise sphingomyelin and cholesterol, a liposomal interior having a pH less than that of the liposomal exterior, and a therapeutic compound contained in the liposome for delivery to the host or a pharmaceutically acceptable salt thereof. The pH gradient may be generated by a methylammonium or ethanolammonium concentration gradient. Typically the cholesterol will be present in the liposomal composition at a total molar proportion of 30% to 50%, and more preferably the sphingomyelin and cholesterol are present at a ratio of about 75/25 mol%/mol%, respectively to 30/50 mol%/mol%, respectively. The delivery of an alkaloid compound such as vincristine or swainsonine, or the antibacterial ciprofloxacin, is particularly suitable in these methods. Vincristine and swainsonine may be present at a drug to lipid ratio of approximately 0.01/1.0 to 0.2/1.0 (wt/wt) and 0.01/1.0 to 0.5/1.0 (mol/mol), respectively. In any event, the liposomal composition containing the drug may be administered repeatedly to the host to maintain a concentration of the drug sufficient to inhibit or treat the disease, e.g., a tumor, but less than an amount which causes unacceptable toxicity to the host. Administration may be by a variety of routes, but the alkaloids are preferably given intravenously or parenterally. Swainsonine is conveniently administered orally. The liposomes administered to the host may be unilamellar, having a mean diameter of 0.05 to 0.45 microns, more preferably from 0.05 to 0.2 microns.

Drawing Description Text (3):
FIGS. 2A and FIG. 2B illustrate the amount of lipid remaining in circulation in BDF1 mice injected with large unilamellar liposomes of DSPC/Chol (55/45, mol/mol) (.largecircle.), SM/Chol (55/45, mol/mol) (.circle-solid.) or SM/Chol/PEG-PE (55/40/5, mol/mol/mol) (.box-solid.). Injected liposomes were either empty (FIG. 2A) or loaded with vincristine at a drug/lipid ratio of approximately 0.1 (FIG. 2B). The injected dose of lipid was 20 mg/kg, corresponding to a total injection of approximately 430 .mu.g of lipid.

Drawing Description Text (4):
FIG. 3 depicts the vincristine/lipid ratio in the plasma of BDF1 mice at various times after the injection of large unilamellar liposomes of DSPC/Chol (55/45, mol/mol) (.largecircle.), SM/Chol (55/45, mol/mol) (.circle-solid.) or SM/Chol/PEG-PE (55/40/5, mol/mol/mol) (.box-solid.). Mice were injected with liposomes at a vincristine/lipid ratio of approximately 0.1, corresponding to a lipid dose of 20 mg/kg and a vincristine dose of 2.0 mg/kg. Total amounts injected were approximately 430 .mu.g of lipid and 43 .mu.g of vincristine.

Drawing Description Text (5):
FIG. 4 shows the total vincristine remaining in the plasma of BDF1 mice at various times after the injection of large unilamellar liposomes of DSPC/Chol (55/45, mol/mol) (.largecircle.), SM/Chol (55/45, mol/mol) (.circle-solid.) or SM/Chol/PEG-PE (55/40/5, mol/mol/mol) (.box-solid.). Mice were injected with liposomes at a vincristine/lipid ratio of approximately 0.1, corresponding to a lipid dose of 20 mg/kg and a vincristine dose of 2.0 mg/kg. Total amounts injected were approximately 430 .mu.g of lipid and 43 .mu.g of vincristine.

Drawing Description Text (7):
FIG. 6 depicts the loading of vincristine in P388 tumors. Delivery of vincristine to peritoneal P388 tumors in BDF1 mice after i.v. injection of large unilamellar liposomes of DSPC/Chol (55/45. mol/mol) (.largecircle.), SM/Chol (55/45, mol/mol) (.circle-solid.) or SM/Chol/PEG-PE (55/40/5, mol/mol/mol) (.box-solid.) containing vincristine at a drug/lipid ratio of 0.1 (wt/wt). Vincristine was injected at a dose of 20 mg/kg, representing a lipid dose of 20 mg/kg.

Drawing Description Text (8):
FIGS. 7A-7C show collectively the anti-tumor efficacy of liposomal formulations of vincristine. BDF1 mice containing P388 tumors were injected with large unilamellar liposomes of DSPC/Chol (55/45, mol/mol) (.gradient.), SM/Chol (55/45, mol/mol) (.quadrature.) or SM/Chol/PEG-PE (55/40/5, mol/mol/mol) (.DELTA.) containing vincristine at a drug/lipid ratio of 0.1 (wt/wt). Control mice received no injection (.circle-solid.). Liposome concentrations prior to injection were adjusted to achieve vincristine dosages of 1.0 (FIG. 7A), 2.0 (FIG. 7B) and 4.0 (FIG. 7C) mg/kg.

Drawing Description Text (12):
FIGS. 11A and 11B show vincristine levels in (A) plasma and (B) tumors after administration of free and liposomal vincristine in SCID mice bearing A431 tumors. SCID mice bearing two A431 tumors were injected i.v. with free vincristine (.quadrature.) or with large unilamellar liposomes of DSPC/Chol (.largecircle.) or SM/Chol (.circle-solid.) containing vincristine at a drug/lipid ratio of 0.1 (wt/wt). Vincristine was injected at a dose of 2.0 mg/kg, representing a lipid of dose of 20 mg/kg. Data represent means (.+-.standard error) of three mice (6 tumors); where standard error bars are not visible, they are smaller than the size of the symbol.

Drawing Description Text (13):
FIG. 12 shows antitumor efficacy of free and liposomal vincristine in SCID mice bearing A431 tumors. SCID mice bearing two A431 tumors received no treatment (.circle-solid.) or were injected i.v. with free vincristine (.quadrature.) or with large unilamellar liposomes of DSPC/Chol (.largecircle.) or SM/Chol (.circle-solid.) containing vincristine at a drug/lipid ratio of 0.1 (wt/wt). Vincristine was injected at a dose of 2.0 mg/kg, representing a lipid of dose of 20 mg/kg. Data represent the weight of A431 tumors (expressed as the percent of the tumor weight immediately prior to treatment) and are the means (.+-.standard error) of 8-10 tumors in 4-5 mice.

Detailed Description Text (2):
The present invention provides compositions and methods for enhanced delivery of therapeutic compounds to a host. The liposomal formulations of the invention have extended circulation lifetimes and/or enhanced drug retention. The liposomes, also referred to as "sphingosomes," are comprised of sphingomyelin and cholesterol and have an acidic intraliposomal pH. The liposomal formulations based on sphingomyelin and cholesterol have several advantages when compared to other formulations. The sphingomyelin/cholesterol combination produces liposomes which are much more stable to acid hydrolysis, have significantly better drug retention characteristics, have better loading characteristics into tumors and the like, and show significantly better anti-tumor efficacy than other liposomal formulations which were tested.

Detailed Description Text (5):
A wide variety of therapeutic compounds may be delivered by the liposomes and methods of the present invention. "Therapeutic compound" is meant to include, e.g., nucleic acids, proteins, peptides, oncolytics, anti-infectives, anxiolytics, psychotropics, immunomodulators, ionotropes, toxins such as gelonin and inhibitors of eucaryotic protein synthesis, and the like. Preferred among the therapeutic compounds for entrapment in the liposomes of the present invention are those which are lipophilic cations. Among these are therapeutic agents of the class of lipophilic molecules which are able to partition into the lipid bilayer phase of the liposome, and which therefore are able to associate with the liposomes in a membrane form. Representative drugs include prostaglandins, amphotericin B, methotrexate, cis-platin and derivatives, vincristine, vinblastine, progesterone, testosterone, estradiol, doxorubicin, epirubicin, beclomethasone and esters, vitamin E, cortisone, dexamethasone and esters, betamethasone valerete and other steroids, etc.

Detailed Description Text (6):
Particularly preferred therapeutic compounds for use in the present invention is the fluorinated quinolone antibacterial ciprofloxacin and its derivatives, and the alkaloid compounds and their derivatives. Among the alkaloid derivatives are swainsonine and members of the vinca alkaloids and their semisynthetic derivatives, such as, e.g., vinblastine, vincristine, vindesin, etoposide, etoposide phosphate, and teniposide. Among this group, vinblastine and vincristine, and swainsonine are particularly preferred. Swainsonine (Creaven and Mihich, Semin. Oncol. 4:147 (1977) has the capacity to stimulate bone marrow proliferation (White and Olden, Cancer Commun. 3:83 (1991)). Swainsonine also stimulates the production of multiple cytokines including IL-1, IL-2, TNF, GM-CSF and interferons (Newton, Cancer Commun. 1:373 (1989); Olden, K., J. Natl. Cancer Inst., 83:1149 (1991)). It also reportedly induces B- and T-cell immunity, natural killer T-cell and macrophage-induced destruction of tumor cells in vitro and, when combined with interferon, has direct anti-tumor activity against colon cancer and melanoma cancers in vivo (Dennis, J., Cancer Res., 50:1867 (1990); Olden, K., Pharm. Ther. 44:85 (1989); White and Olden, Anticancer Res., 10:1515 (1990)). Other alkaloids useful in the present invention include paclitaxel (taxol) and synthetic derivatives thereof.

Detailed Description Text (11):
Before or after sizing, the external pH of the liposome preparation is increased to about pH 7.0 to 7.5, by the addition of suitable buffer, e.g., 0.5M Na.sub.2 HPO.sub.4. The drug or drugs of choice are then admixed with the liposomes at an appropriate concentration, e.g., a vincristine/lipid ratio of 0.01/1.0 to 0.2/1.0 (wt/wt), for a time and under conditions sufficient to allow transmembrane uptake of the drug(s), e.g., from about 5 to 30 min. or more and at about 45.degree.-65.degree. C. (e.g., 10 min. at 60.degree. C. in the case of the liposomal vincristine preparations described in the Examples below), although one of ordinary skill in the art will understand that the conditions may be adjusted and uptake monitored accordingly. The formulation of liposomes and therapeutic compound(s) should generally consist of a relatively uniform population of vesicles in terms of size and drug-lipid ratio.

Detailed Description Text (24):
Large unilamellar liposomes of DSPC/Chol or SM/Chol were prepared as described above in 0.3M citrate buffer at pH 2.0 and were then diluted to 3.2 mg/ml of lipid. The liposomes were incubated at 37.degree. C. for various times then frozen prior to the determination of lipid hydrolysis. Lipid dispersions were thawed then the lipid extracted into CHCl.sub.3 /CH.sub.3 0H and concentrated under a stream of nitrogen gas. Known quantities of lipid were spotted onto K6F thin layer chromatography plates and developed in CHCl.sub.3 /CH.sub.3 /OH/H.sub.2 O/NH.sub.4 OH (65/25/4/0.3, by volume). Lipids were visualized in iodine vapor then the appropriate regions of the plate were recovered and analyzed for phosphorous

according to Bartlett, J. Biol. Chem. 234:466-468 (1959), incorporated herein by reference. Total hydrolysis of DSPC was determined from the amount of MSPC present in the samples and then corrected to total hydrolysis; hydrolysis of sphingomyelin was calculated from the difference between the amount of lipid chromotographed and that recovered as non-hydrolyzed sphingomyelin. Calibration curves were determined for each of DSPC, MSPC and sphingomyelin.

Detailed Description Text (29):
Uptake of vincristine into large unilamellar liposomes was achieved using a pH gradient-dependent procedure described by Mayer et al., Cancer Chemother. Pharmacol. 33:17-24 (1993), incorporated herein by reference. Briefly, a solution of vincristine sulfate (Oncovin.RTM., Eli Lilly, Indianapolis, Ind.) was added to liposomes at a drug/lipid ratio of 0.1/1 (wt/wt) and equilibrated at 60.degree. C. for 5 to 10 minutes. Vincristine uptake in response to a transmembrane pH gradient was initiated by the addition of 0.5M Na.sub.2 HPO.sub.4 to bring the external pH to 7.2-7.6. Uptake was allowed to proceed for 10 minutes at 60.degree. C. and typically had a trapping efficiency of approximately 95% (Mayer et al., Cancer Chemother. Pharmacol. 33:17-24 (1993)).

Detailed Description Text (30):
Liposomes of DSPC/Chol (55/45), SM/Chol (55/45) or SM/Chol/PEG-PE (55/40/5) containing the non-exchangeable and non-metabolized radiolabel .sup.14 C-CHDE (cholesteryl-4-hexadecyl ether radiolabeled with .sup.3 H or .sup.14 C, as indicated, obtained from New England Nuclear) were prepared. Empty liposomes or liposomes loaded with .sup.3 H-vincristine (Amersham) were diluted to the indicated concentration with HBS then injected intravenously into BDF1 mice (8-10 weeks old; Charles River) at a vincristine dose of 2 mg/kg (lipid dose of 20 mg/kg). At various times following the liposome injection, blood was obtained by heart puncture and liver, spleen and muscle recovered. In all cases, lipid and vincristine distributions were determined by liquid scintillation counting of known volumes of plasma and 10% homogenates of the tissues.

Detailed Description Text (31):
The clearance of empty liposomes of DSPC/Chol and SM/Chol is shown in FIG. 2A. Liposomes composed of SM/Chol were removed from circulation at a slightly slower rate than were DSPC/Chol liposomes. This difference in clearance rates between DSPC/Chol liposomes and SM/Chol liposomes was also observed in formulations containing vincristine, as shown in FIG. 2B, although the overall clearance rates were slower in the presence of vincristine due to the effect of the drug on RES activity. The amount of SM/Chol remaining in circulation was typically 30-50% higher than for DSPC/Chol liposomes. A further increase in the amount of lipid in circulation was achieved by the addition of 5 mol% PEG-PE to the SM/Chol mixtures; 24 hours after i.v. injection, 200 .mu.g lipid/ml plasma remained in circulation for SM/Chol/PEG-PE liposomes compared with 100 .mu.g/ml plasma for SM/Chol liposomes and 65 .mu.g/ml plasma for DSPC/Chol liposomes (FIG. 2B).

Detailed Description Text (32):
The drug retention characteristics of the liposomes were significantly altered by changes in the lipid composition of the vesicles. Vincristine leakage from DSPC/Chol liposomes was very rapid, with only 50% of the originally encapsulated vincristine remaining entrapped after 4 hours in circulation, as shown in FIG. 3. In contrast, vincristine leakage from SM/Chol liposomes was much slower, with greater than 60% of the entrapped drug remaining in the liposomes 24 hours after injection (FIG. 3). Furthermore, additional increases in the retention of vincristine in SM/Chol liposomes were not observed in the presence of a two-fold greater transmembrane pH gradient (i.e., phi.sub.i =2.0). The presence of 5 mol% PEG-PE in SM/Chol liposomes caused a significant increase in the permeability of vincristine; approximately 30% of the entrapped vincristine remained in the liposomes after 24 hours in circulation, as shown in FIG. 3.

Detailed Description Text (33):
Anti-tumor efficacy of liposomal vincristine is a function of the amount of the drug remaining in circulation and, therefore, is a consequence of both liposome longevity in circulation and drug retention within the liposomes. The total amount of vincristine remaining in circulation was significantly lower in the liposomal DSPC/Chol formulations than in either the liposomal SM/Chol or SM/Chol/PEG-PE formulations, as shown in FIG. 4. Both sphingomyelin-based liposome formulations had identical amounts of vincristine remaining in circulation. This was a consequence of the higher vincristine/lipid ratio in SM/Chol than in SM/Chol/PEG-PE (FIG. 3) and the lower amount of lipid remaining in circulation in SM/Chol than in SM/Chol/PEG-PE (FIG. 2B).

Detailed Description Text (37):
Thus, from this Example it can be seen that liposomes composed of SM/Chol had circulation lifetimes slightly longer than similar DSPC/Chol liposomes, both in the presence and absence of entrapped vincristine (FIG. 2). SM/Chol liposomes were dramatically better than DSPC/Chol liposomes at retaining vincristine that had been encapsulated using the transmembrane pH gradient method (FIG. 4). The addition of PEG-PE to SM/Chol liposomes significantly increased the circulation longevity of the liposomes, but PEG-PE also caused a significant increase in the leakage of vincristine from the liposomes. The increased levels of vincristine remaining in circulation in SM/Chol and SM/Chol/PEG-PE liposomal formulations (FIG. 4) was a consequence of both improved drug retention in SM-containing liposomes (FIG. 3) and the increased circulation longevity of SM/Chol/PEG-PE liposomes (FIG. 2b). However, the increased circulation lifetimes of SM/Chol/PEG-PE liposomes were balanced by the lower drug retention by liposomes containing PEG-PE. Therefore, in SM-based liposomal formulations of vincristine, there was no improvement in vincristine circulation longevity by the addition of the lipid PEG-DSPE (FIG. 4). Furthermore, since there was no improvement in vincristine retention in vivo by the use of a phi.sub.i =2.0, the optimal vincristine retention in circulation was achieved with a relatively simple liposomal formulation comprised of only sphingomyelin, cholesterol and citrate buffer (pH 4.0).

Detailed Description Text (39):
Tumor Loading Of Liposomal Vincristine

Detailed Description Text (40):
To determine whether increased vincristine longevity in circulation, as shown in FIG. 4, resulted in increased drug delivery to tumors, the loading of liposomal vincristine into P388 tumors was examined. For tumor loading experiments, BDF1 mice were injected i.p. with 10.sup.6 P388 cells (obtained from National Cancer Institute, Bethesda, Md.) (passaged weekly in BDF1 mice) 24 hrs prior to the liposome injection. At various times following the liposome injection the tumor was recovered by peritoneal lavage. In all cases, lipid and vincristine distributions were determined by liquid scintillation counting of known volumes of lavage.

Detailed Description Text (41):
As shown in FIG. 6, accumulation of vincristine from DSPC/Chol liposomes in P388 tumors had an early peak at 4 hours after liposome injection and was significantly lower at later times. In contrast, vincristine from formulations of both SM/Chol and SM/Chol/PEG-PE showed sustained delivery of vincristine for up to 24 to 48 hours after liposome injection. That is, SM/Chol and SM/Chol/PEG-PE formulations of vincristine delivered at least 30% more vincristine to P388 tumors than did DSPC/Chol liposomes.

Detailed Description Text (42):
The increased levels of vincristine remaining in circulation in the plasma using SM-based liposomal formulations (FIG. 4) was reflected in greater amounts of vincristine loaded to P388 tumors (FIG. 6). This relationship suggests, for P388 tumors in BDF1 mice, that liposomes containing DSPC, SM and/or PEG-PE are not

significantly different in their ability to extravasate from circulation to the peritoneal tumor.

Detailed Description Text (44):
In Vivo Efficacy of Liposomal Vincristine Against P388 Tumors

Detailed Description Text (45):
To determine whether increased delivery of vincristine to P388 tumors by SM/Chol and SM/Chol/PEG-PE liposomes, as shown in Example III, resulted in increased anti-tumor activity, the efficacy of liposomal formulations of vincristine was determined.

Detailed Description Text (46):
BDF1 mice bearing P388 tumors were treated with liposomal formulations of DSPC/Chol (55/45) mol/mol), SM/Chol (55/45, mol/mol) or SM/Chol/PEG-PE (55/40/5, mol,mol,mol) containing vincristine at a drug/lipid ratio of 0.1 (wt/wt).

Detailed Description Text (47):
Large unilamellar liposomes of DSPC/Chol (55/45), SM/Chol (55/45) and SM/Chol/PEG-PE (55/40/5) were prepared as described above and loaded with vincristine at a vincristine/lipid ratio of 0.1/1 (wt/wt). Liposomal vincristine was injected i.v. into BDF1 mice that had been administered 24 hours earlier with an i.p. injection of 10.sup.6 P388 cells. Liposome concentration was adjusted to achieve vincristine dosages of 1.0, 2.0 and 4.0 mg/kg, then animal weights and survival was followed during the subsequent 60 days. Animals surviving for 60 days were re-injected with 10.sup.6 P388 cells to evaluate the immune component of long-term survival.

Detailed Description Text (48):
As shown in FIG. 7, control mice that received no injection of liposomal vincristine survived 10-11 days after administration of the P388 tumor. Treatment with either DSPC/Chol or SM/Chol/PEG-PE formulations at a vincristine dosage of 1 mg/kg increased the survival time to 17 and 19 days, respectively. Treatment with SM/Chol formulations at the same vincristine dosage gave a slight improvement in survival, 23 days.

Detailed Description Text (49):
At a vincristine dosage of 2 mg/kg, both DSPC/Chol and SM/Chol/PEG-PE formulations increased survival to 30-31 days. In contrast, at this vincristine dosage, the SM/Chol formulation was significantly more effective; 60% of the mice were surviving at 60 days after administration of the P388 tumor (FIG. 7). At a vincristine dosage of 4 mg/kg, both the DSPC/Chol and SM/Chol/PEG-PE formulations gave 40% of the mice surviving at 60 days after P388 tumor injection. Formulations of SM/Chol were significantly more efficacious; apart from a single vincristine toxicity death, survival of the remaining mice at 60 days was 100% (FIG. 7).

Detailed Description Text (50):
Thus, the antitumor efficacy of SM/Chol liposomes was significantly better than that of SM/Chol/PEG-PE liposomes (FIG. 7) despite the observation that the loading of vincristine to P388 tumors was identical in these two liposomal formulations (FIG. 6). This result suggests that the better vincristine retention properties of SM/Chol liposomes in circulation, compared to SM/Chol/PEG-PE liposomes (FIG. 3), may also occur in the peritoneal cavity and result in improved vincristine uptake by the P388 tumor cells. Formulations of SM/Chol were approximately two-fold more effective than were the formulations based on either DSPC/Chol or SM/Chol/PEG-PE. That is, survival achieved by DSPC/Chol and SM/Chol/PEG-PE formulations at vincristine dosages of 2.0 mg/kg were attained by SM/Chol at a dosage of 1.0 mg/kg. Similarly, the survival obtained by DSPC/Chol and SM/Chol/PEG-PE at a dose of 4.0 mg/kg of vincristine was very similar to that achieved by SM/Chol formulations at 2.0 mg/kg.

Detailed Description Text (53):
Female Balb/c mice, 5-6 weeks of age, were housed under standard conditions. The animals received free access to both food and water throughout the experiment after a one week acclimatization period prior to experimental manipulation. Swainsonine (Toronto Res. Chem.) was radiolabeled with tritium. Tritiated swainsonine was administered as a lipid-based formulation (L-Im) and as an aqueous formulation containing the free drug (F-Im). Tritiated swainsonine was loaded into sphingomyelin/cholesterol (Avanti Polar Labs) sphingosomes using a citrate buffer pH 2 gradient at a drug-to-lipid ratio of 0.2:1 (mol:mol) and with an efficiency of loading of 80%. Two hundred microliters of the lipid and aqueous swainsonine formulations were given orally by gavage (p.o.), intraperitoneally (i.p.), or intravenously (i.v.). Fifty microliter blood samples were collected by retroorbital bleeds at 1, 3, 6, and 24 hours after administration. The blood samples were bleached and then counted in a scintillation counter. Results were expressed as the percentage of the administered dose in the blood at various time-points after administration.

Detailed Description Text (67):
Tumor loading and antitumor efficacy properties of DSPC/Chol and SM/Chol liposomal formulations of vincristine were determined in mice bearing solid human A431 squamous cell xenograft tumors. These experiments were undertaken to ensure that the positive results observed in the murine ascitic P388 tumor model were representative of other tumor types. SCID mice bearing 100-200 mg solid human A431 tumors were injected i.v. with free vincristine or with liposomes of either DSPC/Chol or SM/Chol containing vincristine. Vincristine encapsulated DSPC/Chol and SM/Chol liposomes were prepared as in Example II. Encapsulation of vincristine in DSPC/Chol and SM/Chol liposomes increased the amount of vincristine remaining in circulation 24 hours after administration by 28- and 87-fold, respectively, compared with free vincristine (FIG. 11A). As observed in BDF1 mice bearing P388 tumors, the amount of vincristine remaining in the circulation in SM/Chol liposomes at 24 hours after injection was approximately 3-fold greater than for vincristine encapsulated in DSPC/Chol liposomes (FIG. 11A).

Detailed Description Text (68):
Improved vincristine circulation longevity correlated with increases in the loading of vincristine in the A431 tumors (FIG. 11A). Specifically, free vincristine levels in the A431 tumors were highest (0.856 mg/g tumor) at 0.5 hours after injection and decreased to 0.32 mg/g tumor at 24 hours (FIG. 11B). Encapsulation of vincristine in DSPC/Chol liposomes increased the amount of vincristine in A431 tumors at 4 to 48 hours after administration to 1.3-1.55 mg/g tumor, respectively (FIG. 11B). Encapsulation of vincristine in SM/Chol liposomes resulted in a further increase in vincristine delivery to A431 tumors at 24 to 48 hours after injection to 2.8-3.2 mg/g tumor, representing a 2-fold increase in the delivery obtained with DSPC/Chol liposomes. As observed in the murine ascitic tumor model, the vincristine/lipid observed in the solid human A431 tumors were very similar to those observed in the plasma. That is, for vincristine encapsulated in DSPC/Chol liposomes, the vincristine/lipid (wt/wt) ratios at 24 hours after injection were 0.022 in the plasma and 0.029 in the tumor, while for vincristine encapsulated in SM/Chol liposomes the vincristine/lipid ratios were 0,055 in the plasma and 0.050 in the tumor.

Detailed Description Text (69):
The antitumor efficacy of free and liposomal vincristine against A431 was closely correlated with vincristine accumulation at the tumor site (FIG. 12). SCID mice bearing the A431 tumors that received no treatment showed a 100% increase in tumor weight within 4-5 days after treatment was initiated and required termination within 10 days when the tumor exceeded 10% of the total body weight. Tumor bearing SCID mice treated with free vincristine at 2.0 mg/kg had a brief delay in tumor growth (100% increase in tumor weight achieved within 6-8 days) but required termination between 10-12 days. In contrast, treatment with vincristine

encapsulated in DSPC/Chol liposomes resulted in a significant delay in tumor growth (100% increase in tumor weight at 15-20 days, termination at 21 days after treatment). This therapy was further enhanced by a single treatment of vincristine encapsulated in SM/Chol liposomes. In this treatment group a small but consistent decrease in tumor size was observed. At 15 days after injection, several tumors were palpable but unmeasurable and by 33 days after treatment several tumors were not palpable. Of the five mice (total of 10 tumors) treated with SM/Chol liposomal vincristine, 1 animal was terminated early due to tumor ulceration, not due to tumor growth. Of the eight tumors remaining at 40 days after liposome injection, histological analysis indicated that all eight tumors were actively dividing squamous cell carcinomas of a mass undetectable by physical examination. Therefore, treatment with SM/Chol liposomal vincristine effected a significant reduction in tumor growth, although none of the original tumors were cured.

Detailed Description Text (84):
In summary, the present invention demonstrates that liposomal formulations of ciprofloxacin, vincristine and other alkaloids based on sphingomyelin/cholesterol vesicles have several significant advantages over formulations based on DSPC/cholesterol vesicles. Specifically, formulations based on sphingomyelin/cholesterol: (1) are much more stable to acid hydrolysis, (2) have significantly better drug retention characteristics, (3) have better tumor loading characteristics, and (4) show significantly better anti-tumor efficacy than do comparable liposomes composed of DSPC/Chol or SM/Chol/PEG-PE.

Other Reference Publication (7):
Mayer et al., "Liposomal Vincristine Preparations Which Exhibit Decreased Drug Toxicity and Increased Activity against Murine L1210 and P388 Tumors," Cancer Res. 50:575-579 (Feb. 1, 1990).

Other Reference Publication (12):
Mayer et al., "Identification of Vesicle Properties that Enhance the Antitumour Activity of Liposomal Vincristine Against Murine L1210 Leukemia," Cancer Chemother. Pharmacol. 33:17-24 (1993).

Other Reference Publication (14):
Boman et al., "Liposomal Vincristine Which Exhibits Increased Drug Retention and Increased Circulation Longevity Cures Mice Bearing P388 Tumors," Cancer Res. 54: 2830-2833 (Jun. 1, 1994).

CLAIMS:

6. The liposomal composition of claim 5 wherein the alkaloid is selected from vincristine, vinblastine, swainsonine or etoposide or prodrugs thereof.

7. The liposomal composition of claim 6, wherein the alkaloid is vincristine.

9. The liposomal composition of claim 6, wherein vincristine is present at a drug to lipid ratio of approximately 0.01/1.0 to 0.2/1.0 (wt/wt) and swainsonine is present at a drug to lipid ratio of 0.01/1.0 to 0.5/1.0 (mol/mol) .

19. The method of claim 16, wherein the alkaloid compound is vincristine or swainsonine.

20. The method of claim 19, wherein the alkaloid compound is vincristine.

22. The method of claim 19, wherein vincristine is present in the liposomal composition at a drug to lipid ratio of approximately 0.01/1.0 to 0.2/1.0 (wt/wt) and swainsonine is present at a drug to lipid ratio of 0.01/1.0 to 0.5/1.0 (mol/mol).

Previous Doc Next Doc Go to Doc#

Hit List

Clear | Generate Collection | Print | Fwd Refs | Bkwd Refs | Generate OACS

Search Results - Record(s) 1 through 4 of 4 returned.

☐ 1. Document ID: US 6410328 B1

Using default format because multiple data bases are involved.

L4: Entry 1 of 4 File: USPT Jun 25, 2002

US-PAT-NO: 6410328
DOCUMENT-IDENTIFIER: US 6410328 B1

TITLE: Sensitizing cells to compounds using lipid-mediated gene and compound delivery

DATE-ISSUED: June 25, 2002

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Maclachlan; Ian	Vancouver			CA
Buchkowsky; Susan S.	Vancouver			CA
Graham; Roger W.	Vancouver			CA

US-CL-CURRENT: 435/458; 424/93.2, 435/320.1, 435/455, 514/44

Full | Title | Citation | Front | Review | Classification | Date | Reference | | | Claims | KWIC | Draw De

☐ 2. Document ID: US 5814335 A

L4: Entry 2 of 4 File: USPT Sep 29, 1998

US-PAT-NO: 5814335
DOCUMENT-IDENTIFIER: US 5814335 A

TITLE: Sphingosomes for enhanced drug delivery

DATE-ISSUED: September 29, 1998

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Webb; Murray S.	Vancouver			CA
Bally; Marcel B.	Bowen Island			CA
Mayer; Lawrence D.	N. Vancouver			CA
Miller; James J.	Vancouver			CA
Tardi; Paul G.	Richmond			CA

US-CL-CURRENT: 424/450

Full | Title | Citation | Front | Review | Classification | Date | Reference | Claims | KWIC | Draw De

☐ 3. Document ID: US 5741516 A

L4: Entry 3 of 4 File: USPT Apr 21, 1998

US-PAT-NO: 5741516
DOCUMENT-IDENTIFIER: US 5741516 A

TITLE: Sphingosomes for enhanced drug delivery

DATE-ISSUED: April 21, 1998

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Webb; Murray S.	Vancouver			CA
Bally; Marcel B.	Bowen Island			CA
Mayer; Lawrence D.	N. Vancouver			CA
Miller; James J.	Vancouver			CA
Tardi; Paul G.	Richmond			CA

US-CL-CURRENT: 424/450; 514/27, 514/283

Full | Title | Citation | Front | Review | Classification | Date | Reference | Claims | KWIC | Draw De

☐ 4. Document ID: US 5543152 A

L4: Entry 4 of 4 File: USPT Aug 6, 1996

US-PAT-NO: 5543152
DOCUMENT-IDENTIFIER: US 5543152 A

TITLE: Sphingosomes for enhanced drug delivery

DATE-ISSUED: August 6, 1996

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Webb; Murray S.	Vancouver			CA
Bally; Marcel B.	Bowen Island			CA
Mayer; Lawrence D.	North Vancouver			CA

US-CL-CURRENT: 424/450; 514/27, 514/283

Full | Title | Citation | Front | Review | Classification | Date | Reference | Claims | KWIC | Draw De

Clear | Generate Collection | Print | Fwd Refs | Bkwd Refs | Generate OACS

Terms	Documents
L3 and sphingomyelin	4

Display Format: - Change Format

Previous Page Next Page Go to Doc#

Hit List

Clear | Generate Collection | Print | Fwd Refs | Bkwd Refs | Generate OACS

Search Results - Record(s) 1 through 1 of 1 returned.

☐ 1. Document ID: JP 60155119 A

Using default format because multiple data bases are involved.

L2: Entry 1 of 1 File: JPAB Aug 15, 1985

PUB-NO: JP360155119A
DOCUMENT-IDENTIFIER: JP 60155119 A
TITLE: SUBSTANCE INDUCTING PRODUCTION OF ANTIBODY

PUBN-DATE: August 15, 1985

INVENTOR-INFORMATION:

NAME	COUNTRY
YAMASHINA, IKUO	

US-CL-CURRENT: 424/450; 436/829
INT-CL (IPC): A61K 31/70; A61K 35/12; A61K 35/54; A61K 37/00; A61K 39/39; C07C 103/66; C07F 9/10; C07K 17/00; C07H 13/04

Full | Title | Citation | Front | Review | Classification | Date | Reference | Claims | KWIC | Draw De

Clear | Generate Collection | Print | Fwd Refs | Bkwd Refs | Generate OACS

Terms	Documents
(liposome) same (precipitat$) same sphingomyelin	1

Display Format: - Change Format

Previous Page Next Page Go to Doc#

Hit List

Clear | Generate Collection | Print | Fwd Refs | Bkwd Refs | Generate OACS

Search Results - Record(s) 1 through 1 of 1 returned.

☐ 1. Document ID: US 6740335 B1

Using default format because multiple data bases are involved.

L4: Entry 1 of 1 File: USPT May 25, 2004

US-PAT-NO: 6740335
DOCUMENT-IDENTIFIER: US 6740335 B1

TITLE: Liposomal camptothecin formulations

DATE-ISSUED: May 25, 2004

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Moynihan; Karen Lewis	Redlands	CA		
Emerson; David Lloyd	Longmont	CO		
Chiang; Su-Ming	West Hills	CA		
Hu; Ning	San Gabriel	CA		

US-CL-CURRENT: 424/450; 264/4.1, 264/4.3

Full | Title | Citation | Front | Review | Classification | Date | Reference | | | Claims | KWIC | Draw D

Clear | Generate Collection | Print | Fwd Refs | Bkwd Refs | Generate OACS

Terms	Documents
(liposome) adj10 (precipitat$) same camptothecin	1

Display Format: - Change Format

Previous Page Next Page Go to Doc#

Refine Search

Search Results -

Terms	Documents
(liposome) adj10 (precipitat$) same (vinca)	1

Database:
US Pre-Grant Publication Full-Text Database
US Patents Full-Text Database
US OCR Full-Text Database
EPO Abstracts Database
JPO Abstracts Database
Derwent World Patents Index
IBM Technical Disclosure Bulletins

Search: L6

Refine Search

Recall Text | Clear | Interrupt

Search History

DATE: Friday, March 04, 2005 Printable Copy Create Case

Set Name side by side	Query	Hit Count	Set Name result set
DB=USPT,EPAB,JPAB,DWPI,TDBD; PLUR=YES; OP=OR			
L6	(liposome) adj10 (precipitat$) same (vinca)	1	L6
L5	L4 and sphingomyelin	0	L5
L4	(liposome) adj10 (precipitat$) same camptothecin	1	L4
L3	(liposome) adj10 (precipitat$)	752	L3
L2	(liposome) same (precipitat$) same sphingomyelin	1	L2
L1	(liposome) adj10 (precipitat$) same sphingomyelin	0	L1

END OF SEARCH HISTORY